REMARKS/ARGUMENTS

Claims 1-61, 63 and 65 are pending in this application. Claim 61 is objected to and claims 1-60, 63 and 65 are rejected.

In response to the Office Action, claims 1, 17, 22, 23, 24, 32, 33, 45, 46 and 61 are amended. Further, claims 16, 54 and 65 are canceled without prejudice or disclaimer. The claim amendments are all entirely supported by the application as originally filed and thus there is no issue of new matter. Upon entry of this Response into the file of the application, claims 1-15, 17-53, 55-61 and 63, as amended, will be pending in the application. Reconsideration of the application is respectfully requested.

Allowable Subject Matter

Applicants note with appreciation the Examiner's statement in ¶13 on p. 14 of the present Action that claim 61 would be allowable if rewritten or amended to overcome the objection to the claim.

In ¶1 on p. 2 claim 61 is objected to due to the fact that, at line 2, the words "hormone comprising" are run together, i.e., without a space between the words. The claim has thus been amended as suggested by the Examiner and the amendment is believed to overcome the objection, which should therefore be withdrawn. Claim 61 is, thus, now believed to be in condition for allowance.

Rejections Based on 35 U.S.C. §102

Claims 1, 6 and 39 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Balschmidt et al. USP 5,157,021 for the reasons given in ¶8 on pp. 7-8 of the Office Action. The rejection is respectfully traversed.

The reference is cited due to its teaching of, *inter alia*, pharmaceutical compositions comprising insulin in which the carboxylic acid groups present in the side chains at residues A4, A17, B13 and B21 are amidated. In response, applicants have amended independent claim 1 to recite the presence, in the claimed oral pharmaceutical composition, of an absorption enhancer effective to promote bioavailability of the peptide active agent. Applicants submit that the Balschmidt et al. reference does not disclose, as now recited in claim 1, an oral pharmaceutical composition adapted to provide enhanced bioavailability of an orally delivered physiologically

active peptide agent, wherein the composition comprises a therapeutically effective amount of the active peptide, which active peptide is amidated at a location that is not naturally amidated, together with an absorption enhancer effective to promote bioavailability of the active peptide agent. Claims 6 and 39, moreover, each depend from claim 1. Thus, the dependent claims contain all of the features recited in the independent claim. Therefore, claims 6 and 39 are distinguishable over the Balschmidt et al. reference for the same reason(s) as claim 1. The Examiner is thus requested to reconsider and withdraw the rejection under 35 U.S.C. §102(b) of claims 1, 6 and 39 over Balschmidt et al. USP 5,157,021.

Claims 1, 4, 5 and 37 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Habener USP 5,120,712 for the reasons given in ¶9 on p. 8 of the Office Action. The rejection is respectfully traversed.

The reference is cited due to its teaching of, *inter alia*, pharmaceutical compositions comprising GLP-1 analogs that are amidated at the C-terminus. In response applicants have, as noted above, amended independent claim 1 to recite the presence, in the claimed oral pharmaceutical composition, of an absorption enhancer effective to promote bioavailability of the peptide active agent. Applicants submit that the Habener reference does not disclose, as now recited in claim 1, an oral pharmaceutical composition adapted to provide enhanced bioavailability of an orally delivered physiologically active peptide agent, wherein the composition comprises a therapeutically effective amount of the active peptide, which active peptide is amidated at a location that is not naturally amidated, and an absorption enhancer effective to promote bioavailability of the active peptide agent. Claims 4, 5 and 37, moreover, all depend (directly or indirectly) from claim 1 and, thus, the dependent claims contain all of the features recited in the independent claim. Therefore, claims 4, 5 and 37 are also distinguishable over the Habener reference for the same reason(s) as claim 1.

The Examiner is thus requested to reconsider and withdraw the rejection under 35 U.S.C. §102(b) of claims 1, 4, 5 and 37 over Habener USP 5,120,712.

Claims 1, 4, 5, 40 and 41 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Barbier et al. USP 6,110,892 for the reasons given in ¶10 on pp. 8-9 of the Office Action. The rejection is respectfully traversed.

The reference is cited due to its teaching of, *inter alia*, pharmaceutical compositions comprising hPTH(1-31)NH_2. In response, as discussed above, applicants have amended independent claim 1 to recite the presence, in the claimed oral pharmaceutical composition, of an absorption enhancer effective to promote bioavailability of the peptide active agent. Applicants

submit that the Barbier et al. reference does not disclose, as now recited in claim 1, an oral pharmaceutical composition adapted to provide enhanced bioavailability of an orally delivered physiologically active peptide agent, wherein the composition comprises a therapeutically effective amount of the active peptide, which active peptide is amidated at a location that is not naturally amidated, and an absorption enhancer effective to promote bioavailability of the active peptide agent. Furthermore, claims 4, 5, 40 and 41 depend (directly or indirectly) from claim 1 and, thus, the dependent claims contain all of the features recited in the independent claim. Therefore, claims 4, 5, 40 and 41 are also distinguishable over the Barbier et al. reference for the same reason(s) as claim 1. The Examiner is thus requested to reconsider and withdraw the rejection under 35 U.S.C. §102(b) of claims 1, 4, 5, 40 and 41 over Barbier et al. USP 6,110,892.

Claims 1, 4, 5, 40, 42, 45, 47, 58, 60 and 63 are rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Peri et al. published U.S. patent application No. 2004/0023882 for the reasons given in ¶11 on pp. 9-10 of the Office Action. The rejection is respectfully traversed.

The reference is cited due to its teaching of, *inter alia*, pharmaceutical compositions comprising hPTH(1-34) amidated at the C-terminus, including hPTH(1-34)NH_2. In response, applicants have amended independent claim 1 and independent claim 45 to recite that the oral pharmaceutical composition comprises not only a peptide amidated at a location that is not naturally amidated, but also of an absorption enhancer effective to promote bioavailability of the peptide active agent. Applicants submit that the Peri et al. reference does not disclose, as now recited in claims 1 and 45, an oral pharmaceutical composition adapted to provide enhanced bioavailability of an orally delivered physiologically active peptide agent, or a method for enhancing the bioavailability of an orally delivered physiologically active peptide, wherein the composition comprises a therapeutically effective amount of the active peptide, which active peptide is amidated at a location that is not naturally amidated, as well as an absorption enhancer effective to promote bioavailability of the active peptide agent.

As a matter of fact, the reference actually teaches away from the claimed composition and method by teaching, e.g., in paragraph [0059], fourth line and paragraph [0064], p. 5, left-hand column, at lines 9-10, the inclusion of an absorption delaying agent which, obviously, would act the opposite of an absorption enhancer.

Furthermore, claims 4, 5, 40 and 42 all depend (directly or indirectly) from claim 1, while claims 47, 58, 60 and 63 all depend (directly or indirectly) from claim 45 and, thus, the dependent claims contain all of the features recited in the respective independent claims. Therefore, claims 4, 5, 40, 42, 47, 58, 60 and 63 are also distinguishable over the Barbier et al. reference for the same

reasons as claims 1 and 45. The Examiner is thus requested to reconsider and withdraw the rejection under 35 U.S.C. §102(e) of claims 1, 4, 5, 40, 42, 45, 47., 58, 60 and 63 over Peri et al. published US Application No. 2004/0023882.

Rejections Based on 35 U.S.C. §103

Claims 1-8, 12-47, 49-51, 54-60, 54-60, 63 and 65 are rejected in ¶4 on pp. 2-4 of the Office Action under 35 U.S.C. §103 over Stern et al. USP 6,086,918 in view of Habener (USP 5,120,712), Balschmidt et al. (USP 5,157,021), Barbier et al. (USP6,110,892), the European Patent Application No. 878,201 or Neiss et al. (USP 4,804,742). The rejection is respectfully traversed.

The references combined to make this rejection (as well as the additional references combined in support of the other §103 rejections discussed below) have all been extensively discussed in applicants' responses filed on July 10, 2006, May 7, 2007 and May 27, 2008. Those remarks are specifically incorporated by reference into this Response.

The Examiner finds that the Stern '918 reference discloses the oral administration of peptides, whereas the remaining, i.e., 'secondary' references disclose amidated peptides that are amidated at locations that are not naturally amidated. Based on these combined disclosures, the Examiner concludes that it would have been obvious at the time the presently claimed composition and method was discovered to combine the references to achieve the composition and method recited, for example, in applicants' composition and method claims. Applicants respectfully disagree, however, for the reasons below.

Claim 65 is canceled in this Amendment without prejudice or disclaimer. Thus, the above rejection is deemed by applicants to be moot as to that claim.

In response to the rejection of the subject claims over the same combination of references in the previous Office Action dated November 26, 2007 applicants submitted, *inter alia*, a 'Declaration of Inventor William Stern Under 37 C.F.R. §1.132' ("Stern I") with their response filed on May 27, 2008. Applicants argued (see, e.g., pp. 12-13 of the May 27, 2008 Amendment) that the evidence discussed in the declaration was sufficient to overcome the *prima facie* case of 'obviousness' postulated by the Examiner, i.e., as based on the combined disclosure of the references cited by him. The Examiner, however, alleges in the present Office Action (see, e.g., pp. 10-12) that the Stern I declaration is insufficient to overcome the various §103 rejections set forth in the Office Action.

In response, submitted with this Response is a 'Second Declaration of Co-Inventor William Stern Under 37 C.F.R. §1.132" ("Stern II"). The Stern II declaration is provided to address the Examiner's objections to the evidence contained in Stern I.

As detailed in, for example, ¶3 of Stern II, Example 3 at pp. 55-57 of applicants' specification compares the bioavailability of an analog of parathyroid hormone, i.e., PTH 1-34, with and without a C-terminal amide group. The improved bioavailability for the peptide that is amidated at a location that is not naturally amidated is demonstrated in Table 8 on specification p. 57. The Examiner in the present Office Action, however, objects that, although the peptides tested "differ only with respect to their amidation state", they were intraduodenally administered, rather than being orally administered as required by the claims.

In response, however, as explained by the declarant in ¶4 of Stern II, the results obtained by intraduodenal administration of peptides are predictive for the oral administration of peptides as described in the present application. The Examiner states in this regard at p. 11 of the Office Action that, "if Applicants and/or Declarant were to establish that the differences in bioavailability shown for intraduodenal administration were predictive of differences in bioavailability for oral administration, the Examiner agrees that the example would demonstrate unexpected results for the tested peptide, PTH1-34NH_2". Since Dr. Stern has, therefore, made the required showing, applicants respectfully submit that the 'obviousness' rejection has at least been overcome with regard to PTH1-34NH_2. The Examiner, however, notes further on p. 11 of the Office Action that a showing with regard to PTH 1-34NH_2 is not commensurate in scope with claims not limited to the subject peptide, i.e., as in the case of the present claims 1 and 45.

Thus, further in support of the patentability of applicants' generic claims Dr. Stern's declaration (Stern II, see also Stern I) also includes a discussion of the unexpected results achieved with peptides other than PTH1-34NH_2. Luteinizing hormone-releasing hormone provides another example of a peptide with unexpectedly improved results. Claim 61, which is directed to this particular peptide, has been found by the Examiner to be in condition for allowance, subject to correction of a minor typographical error in the claim. As the claim is 'allowable' the subject matter must, therefore, be both novel and unobvious. Further evidence of the 'unobvious' nature of claim 61, and thus of a LHRH peptide amidated at a location that is not naturally amidated, i.e., for purposes of providing improved bioavailability of the peptide, is offered in ¶6 of the Stern II declaration.

As discussed in Stern II, ¶6, Example 4 at pp. 57-59 demonstrates unexpected results attributable to the presence of a C-terminal amide on LHRH. See, e.g., Table 9 on specification p.

59. Dr. Stern states in Stern II that naturally occurring LHRH is not amidated. Example 4 thus provides a comparison between naturally occurring (non-amidated) LHRH and amidated LHRH. Since, as noted, natural LHRH is not amidated, the amidated LHRH is, therefore, "amidated at a location that is not naturally amidated". As also noted in declaration ¶6, the LHRH and amidated-LHRH was administered via the inter-duodenal route. However, as indicated in ¶4 such administration is predictive of the results to be obtained via oral administration. Thus, the results provided by Example 4 provide still more support for the unobviousness of applicants' generic claims.

Even further, as discussed for example in ¶7 of the Stern II declaration, Example 1 provides additional evidence in support of the non-obviousness of applicants' generic claims. The Example compares the bioavailability of an orally delivered glycine-extended salmon calcitonin with that of an amidated salmon calcitonin. The results shown in, e.g., Table 5 on p. 52 of the specification clearly establish that the amidation of a peptide improves its bioavailability, i.e., in comparison to the bioavailability of corresponding peptides without such amidation. The limitation of the peptide being added at a location not naturally amidated was added, as explained further in ¶7 of Stern II, only for the purpose of differentiating the claims with such limitation over the disclosure of prior art describing the administration, via a route other than oral administration, of an amidated peptide, such as is described in the 'secondary' references cited in the rejection(s) under 35 U.S.C. §103. The subject limitation, i.e., that the amidation be at a location where natural amidation does not occur, thus is not required in order to achieve the unobvious results discussed in Stern I & II and the Examples provided with this application.

The sum total of applicants' examples, therefore, as evidenced in the discussion found in Stern II taken in conjunction with Stern I, is to conclusively demonstrate that (as discussed in Stern II, ¶8), the amidation of orally delivered peptides improves the bioavailability of such peptides; and that it would not be obvious to one having an ordinary level of skill in this art to expect improved bioavailability from the use of the peptides and methods as now claimed.

Based on the evidence provided by the declaration and pursuant to the discussion above, therefore, the Examiner is respectfully requested to reconsider and withdraw the §103 rejection of claims 1-8, 12-47, 49-51, 54-60, 54-60 and 63.

In ¶5 on pp. 4-5 claims 5 and 48 are rejected under 35 U.S.C. §103 for obviousness over Stern et al. USP 6,086,918, in view of Habener USP 5,120,712, Barbier et al. (USP 6,110,892), European Patent Application No. 878,201 and Neiss et al. USP 4,804,742 as applied against

claims 1-8, 12-27, 49-51, 54-60, 63 and 65 above, and further in view of Stern et al. USP 5,912,014. The rejection is respectfully traversed.

In response, applicants submit that claims 5 and 48 depend, respectively, from claims 1 and 45. The subject claims are believed to be directed to compositions and methods which provide an unexpected improvement in bioavailability in the case of orally administered peptides which are amidated at a location where they are not naturally amidated. Based, therefore, on the discussion above, and the evidence provided in Stern I & II, the Examiner is respectfully requested to reconsider and withdraw the subject rejection.

In ¶6 on pp. 5-6 claims 1-47, 49-60, 63 and 65 (which has been canceled without prejudice or disclaimer) are rejected under 35 U.S.C. §103 for obviousness over WO 02/043767 (Stern et al.) in view of Habener (USP 5,120,712), Balschmidt et al. (USP 5,157,021), Barbier et al. (USP6,110,892), the European Patent Application No. 878,201 or Neiss et al. (USP 4,804,742). The rejection is respectfully traversed.

In response, the Examiner's attention is again directed to the discussion above as it concerns the showing made in Stern II taken in conjunction with Stern I. As indicated, the evidence of unexpected results thus having been produced, applicants respectfully submit that the evidence is sufficient to overcome the Examiner's determination of *prima facie* obviousness. The Examiner is, therefore, respectfully requested to reconsider and withdraw the rejection of the subject claims under 35 U.S.C. §103.

In ¶7 on pp. 6-7 claims 5 and 48 are rejected under 35 U.S.C. §103 for obviousness over WO 02/043767 (Stern et al.) in view of Habener (USP 5,120,712), Barbier et al. (USP6,110,892), the European Patent Application No. 878,201 or Neiss et al. (USP 4,804,742) as applied against claims 1-47, 49-60, 63 and 65 above and further in view of Stern et al. USP 5,912,014. The rejection is respectfully traversed.

Once again, the evidence of unexpected improvement offered with the compositions and methods of the present invention is believed to overcome the 'obviousness' rejection of the subject claims for the reasons set forth above. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

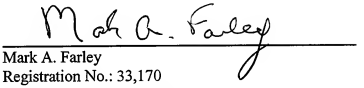
Summary

The claim amendments set forth above, taken in conjunction with the remarks provided herein, as well as the evidence contained in the Second Declaration of Dr. Stern submitted herewith, are believed sufficient to overcome all of the claim objections and rejections set forth in

the Office Action. The Examiner is, therefore, respectfully requested to reconsider and withdraw all of the objections and rejections and to issue a Notice of Allowance for all of the claims, as amended, pending in this application.

THIS CORRESPONDENCE IS BEING SUBMITTED ELECTRONICALLY THROUGH THE PATENT AND TRADEMARK OFFICE EFS FILING SYSTEM ON July 28, 2009.

Respectfully submitted,



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